COPY

PTO/SB/22 (08-03)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless if displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket No. (Optional) PKZ-030

OIPE JC10 MAY 05 2005 PATENT & TRADEMARK OFFICE

RECEIVED MAY 10 2005 TECH CENTER 1600/2900

In re Application of	Stuart B. Levy, *et al.*		
Application Number	09/828456-Conf. #6918	Filed	April 6, 2001
For:	NOVEL BLR MOLECULES AFFECTING ANTIBIOTIC SUSCEPTIBILITY		
Art Unit	1645	Examiner	Jana A. Hines

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate small-entity fee are as follows (check time period desired):

☐	One month (37 CFR 1.17(a)(1))	$
☐	Two months (37 CFR 1.17(a)(2))	$
☒	Three months (37 CFR 1.17(a)(3))	$ 465.00
☐	Four months (37 CFR 1.17(a)(4))	$
☐	Five months (37 CFR 1.17(a)(5))	$

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $ _____ .

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 12-0080 .

I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☒ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a) 43,270

September 4, 2003
Date

Signature

(617) 227-7400
Telephone Number

Megan E. Williams
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below

☐ Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 309882031 US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: September 4, 2003 Signature: _____ (Megan E. Williams)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Application Serial No. 09/828,456
Applicants: Stuart B. Levy, et al
Filed: April 6, 2001
Title: *NOVEL BLR MOLECULES AFFECTING ANTIBIOTIC SUSCEPTIBILITY*
Attorney Docket No.: PKZ-030

Group Art Unit: 1645
Examiner: Hines, Jana A.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

"Express Mail" Mailing Label Number EV 309882031 US

Date of Deposit September 4, 2003

I hereby certify that this transmittal letter and the papers referred to as being enclosed therein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450:

Signature

Megan E. Williams, Esq.
Please Print Name of Person Signing

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Sir:

This is a response to the Office Action dated March 4, 2003 (Paper No. 9). Responsive to the Action, please amend the above-identified application as follows.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the claims are reflected in the listing of the claims which begins on page 5.

Remarks/Arguments begin on page 7.

Amendments to the Specification:

Please replace the paragraph beginning at line 9 of page 3 of the specification with the following amended paragraph:

b) a naturally occurring homolog of a β–lactam-358 (BLR) polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein the naturally occurring homolog is isolated from a pathogenic bacterium and is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule consisting of SEQ ID NO: 1;

Please replace the paragraph bridging pages 20 and 21 of the specification with the following amended paragraph:

Preferably, BLR polypeptides share some amino acid sequence similarity with a polypeptide of SEQ ID NO:2, encoded by a BLR gene set forth in SEQ ID NO:1. The nucleic acid and/or amino acid sequences of an BLR gene or polypeptide (e.g., as provided above) can be used as "query sequence" to perform a search against databases (e.g., either public or private ~~such as http://www.tigr.org~~) to, for example, identify other BLR genes (or polypeptides) having related sequences. For example, such searches can be performed, e.g., using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the above BLR nucleic acid molecules. BLAST polypeptide searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to BLR polypeptide molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. ~~See http://www.ncbi.nlm.nih.gov.~~ See the NCBI web site.

Please replace the paragraph beginning at line 4 of page 33 of the specification with the following amended paragraph:

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A non-limiting example of a mathematical algorithm utilized for comparison of sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST program score=100, wordlength=12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST polypeptide searches can be performed with the XBLAST program, score=50, wordlength =3 to obtain amino acid sequences homologous to the polypeptide molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Research 25(17):3389. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See the NCBI web site ~~http://www.ncbi.nlm.nih.gov~~. Another preferred, non-limiting algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1988). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

Please replace the paragraph bridging pages 34 and 35 of the specification with the following amended paragraph:

The nucleic acid and polypeptide sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify other members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to BLR nucleic acid molecules of the invention. BLAST polypeptide searches can be performed with the XBLAST program, score = 50,

wordlength = 3 to obtain amino acid sequences homologous to BLR polypeptide molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. For example, the nucleotide sequences of the invention can be analyzed using the default Blastn matrix 1-3 with gap penalties set at: existence 11 and extension 1. The amino acid sequences of the invention can be analyzed using the default settings: the Blosum62 matrix with gap penalties set at existence 11 and extension 1. ~~See http://www.ncbi.nlm.nih.gov~~. See the NCBI web site.

Please replace the paragraph bridging pages 34 and 35 of the specification with the following amended paragraph:

Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular compound, but typically include nonionic surfactants (TWEENs™, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Amendments to the Claims:

This listing of the claims will replace all prior versions, and listings, of the claims in the application.

Listing of claims:

1-15. **(Canceled)**

16. **(Currently Amended)** A method for identifying compounds that modulate ~~antibiotic~~ resistance to an antibiotic that affects peptidoglycan synthesis in a ~~microbe~~ bacterium comprising:

contacting a β–lactam-358 (BLR) polypeptide with a test compound;

determining the ability of the test compound to modulate ~~the~~ an activity ~~or expression~~ of a BLR polypeptide as compared to the activity in the absence of the compound, wherein the ability of the compound to modulate the activity of a BRL polypeptide indicates that the test compound modulates resistance to an antibiotic that affects peptidoglycan synthesis; and

selecting those compounds that modulate the activity of the BLR polypeptide to thereby identify compounds that modulate ~~antibiotic~~ resistance to an antibiotic that affects peptidoglycan synthesis.

17. **(Currently Amended)** The method of claim 16, wherein the BLR polypeptide is present in a ~~microbial~~ bacterial cell.

18. **(Currently Amended)** The method of claim ~~16~~17, wherein the BLR polypeptide is heterologous to the cell in which it is present.

19. **(Currently Amended)** The method of claim 17, wherein the ~~microbial~~ bacterial cell is an E. coli cell.

20. **(Currently amended)** The method of claim 17, wherein said step of determining comprises measuring the effect of the test compound on the ability of the ~~microbial~~ bacterial cell to grow in the presence of an antibiotic that affects peptidoglycan synthesis.

21. **(Currently Amended)** The method of claim 20, wherein the ~~antibiotic is an~~ antibiotic that affects peptidoglycan synthesis is selected from the group consisting of: a beta lactam, cycloserine, and bacitracin.

22. **(Currently Amended)** The method of claim ~~21~~16, wherein said step of determining comprises measuring the efflux of the test compound or a marker compound from the cell.

23. **(Currently Amended)** The method of claim 16, wherein the BLR polypeptide is contacted with the test compound in vitro and the ability of the test compound to bind to the BLR polypeptide is determined.

24. **(Currently Amended)** A method for identifying compounds that modulate ~~antibiotic~~ resistance to an antibiotic that affects peptidoglycan synthesis in a ~~microbe~~ bacterium comprising:

contacting an isolated BLR nucleic acid molecule with a test compound;

determining the ability of the test compound to bind to the isolated BLR nucleic acid molecule, wherein the ability of the compound to bind the BRL nucleic acid molecule indicates that the test compound modulates resistance to an antibiotic that affects peptidoglycan synthesis; and

selecting those compounds that bind to the BLR nucleic acid molecule to thereby identify compounds that modulate ~~antibiotic~~ resistance to an antibiotic that affects peptidoglycan synthesis.

25. **(Original)** The method of claim 24, wherein the BLR nucleic acid molecule comprises the nucleotide sequence shown in SEQ ID NO:1.

26. **(Canceled)**

27. **(Canceled)**

28. **(Canceled)**

REMARKS

Claims 16-25 and 27-28 were pending in the application. Claims 21, 27 and 28 have been canceled by the amendments presented herein. Claims 16- 24 have been amended. Accordingly, claims 16-25 will be pending, after the amendments presented herein have been entered. For the Examiner's convenience all of the pending claims are set forth in Appendix A.

Support for the amendments to the claims can be found throughout the specification including the originally filed claims. Specifically, support for the amendments to claims 16- 20, 22 and 24 can be found at, for example, page 1, lines 23-26, and page 16, lines 1-3 of the specification. Further support for the amendments to claims 16 and 24 can be found at page 55, line 1, through page 68, line 20 of the specification.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objections to the Specification

The Examiner has objected to the acronym BLR not being spelled out when used for the first time in the specification.

The Examiner has further objected to the use of embedded hyperlinks and or other forms of browser-executable code in the specification.

These objections are believed to have been rendered moot by the amendments presented herein.

Rejection of Claims 16-25 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 16-25 under 35 U.S.C. § 112, first paragraph as, "containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Examiner is of the opinion that:

> [c]laims 16-25 are drawn to a method for identifying compounds that modulate antibiotic resistance in a microbe comprising a contact step; determination step and selection step which thereby identify compounds that modulate antibiotic resistance. ***The claims are so broad that they encompass determining every modulation of activity in every type of microbe antibiotic resistance,*** however applicants have not described such a method. The instant specification fails to provide a method wherein every modulation of activity or expression of BLR is determined. (*Emphasis Added).*

The Examiner also states:

> [t]he specification does not provide substantive evidence that the claimed method is capable of identifying all compounds that modulate antibiotic resistance in all microbes. This demonstration is required for the skilled artisan to be able to use the claimed method for their intended purpose of identifying compounds that modulate antibiotic resistance in a microbe.

The Examiner further states:

> [t]here is no written description of any method steps which teach such broadly claimed methods. There are no examples that teach by selecting compounds that modulate the activity of the BLP polypeptide, those compounds will further modulate the antibiotic resistance of any type of microbe. The claims fail to recite what medium the method occurs in.

Applicants respectfully traverse this rejection.

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed without undue experimentation.

The amended claims are directed to methods of identifying compounds that modulate resistance to ***an antibiotic that affects peptidoglycan synthesis*** in a ***bacterium***. Applicants teach at pages beginning at pages 56 and 62, respectively, numerous cell-based and cell-free methods for determining if a compound is capable of interacting with and/or modulating the activity of a

BRL polypeptide or nucleic acid molecule. As set forth in the specification, the ability of a compound to modulate a BLR polypeptide activity, (e.g., to modulate virulence, drug resistance, multidrug resistance, or resistance to an antibiotic that affects peptidoglycan synthesis) can be tested by measuring the ability of the compound to affect the resistance phenotype of the microbe to the drug, e.g. by testing the ability of the microbe to grow in the presence of the drug. The specification teaches that such assays can be performed using a standard methods, e.g., an antibiotic disc assay or an automated growth assay. The specification also teaches that the ability of a test compound to modulate the efflux of a drug from the cell can be tested. Applicants teach that cells can be contacted with a test compound with or without an indicator compound (an indicator compound is one which is normally exported by the cell) and that the ability of a test compound to inhibit the activity of an efflux pump can be tested. As taught by Applicants, the activity of an efflux pump can be measured by determining whether the intracellular concentration of the test compound or the indicator compound (e.g., an antibiotic that affects peptidoglycan synthesis or a dye) is elevated in the presence of the test compound. If the intracellular concentration of the indicator compound is increased in the presence of the test compound as compared to the intracellular concentration in the absence of the test compound, then the test compound can be identified as an inhibitor of an efflux pump. With respect to cell-free assays, Applicants teach that a BLR polypeptide or portion thereof can be contacted with a test compound and the ability of the test compound to bind to the BLR polypeptide or biologically active portion thereof is determined. Applicants teach that determining the ability of the BLR polypeptide to bind to a BLR target molecule can also be accomplished using art recognized technology, such as real-time Biomolecular Interaction Analysis (BIA).

Further, Applicants provide in Example 1 a working example of an assay that was used to determine the effect of the BRL polypeptide on bacterial susceptibility to a number of different antibiotics. The working example shows that organisms containing an insertion in the BLR intergenic locus exhibit enhanced resistance to antibiotics that affect peptidoglycan synthesis. Applicants were the first to demonstrate a role of the BLR locus in modulating resistance to antibiotics that affect peptidoglycan synthesis. Given the screening assays described in the specification and the working example provided, the use of BLR molecules in screening assays to identify agents that modulate resistance to antibiotics that affect peptidoglycan synthesis would have been routine.

In response to the assertion that there is no written description in the specification for such broadly claims methods, Applicants have amended the instant claims to be directed to methods of identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis ***in a bacterium***. Applicants submit that such assays are adequately described in the specification and are taught in the working example presented in Example 1. The results of the experiments presented in Example 1 show that the BLR locus affects resistance to antibiotics that affect peptidoglycan synthesis in bacterial cells. Therefore, the instant claims are fully described by the specification.

Applicants believe that based on the teachings in the specification, and the knowledge available to one of ordinary skill on one in the art, an ordinary skilled artisan would have been able to make and use the claimed invention using no more than routine experimentation. Applicants also contend that the instant specification satisfies the written description requirement for the claimed invention as set forth in the Written Description Guidelines (66 Fed. Reg at 1106) and by the court in *Enzo Biochem, Inc. v. Gen-Probe Inc.* (296 F.3d 1316 (Fed. Cir. 2002). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 16-25 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 16-25 under 35 U.S.C. § 112, second paragraph as, "being indefinite for failing to particularly point our and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner is of the opinion that:

> [t]he preamble of the claims is drawn to a method for identifying compounds that modulate antibiotic resistance in a microbe, however the recited steps within the method comprise contacting a BLR polypeptide with a test compound; followed by a determination step; and selection step. There is no correlation step which correlates the modulation of BLR activity to antibiotic resistance in a microbe. Therefore, the goal of the preamble is not commensurate with the steps of the method that are drawn to identifying compounds.

Applicants respectfully traverse the foregoing rejection for the following reasons. The Examiner states that there is no correlation step between the modulation of BLR activity and antibiotic resistance in a microbe. Applicants have amended the claims to recite a correlation step wherein the ability of a compound to bind the BRL nucleic acid molecule, or modulate a

BRL activity, indicates that the test compound modulates resistance to an antibiotic that affects peptidoglycan synthesis. Therefore, Applicants' claims are clear and definite and, accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

The Examiner has further rejected claims 16-25 under 35 U.S.C. § 112, second paragraph. The Examiner is of the opinion that:

> [t]he term "modulates" in claim is a relative term which renders the claim indefinite. The term "modulates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore the metes and bounds of modulates activity cannot be determined, since no specific activity is defined and no specific type of modulation is required.

Applicants respectfully traverse this rejection on the grounds that the claims are clear and definite. First of all, Applicants specification clearly states that modulate means up regulation or down regulation (see, for example, page 30, lines 10-11 of the specification). Also, Applicants further define modulators based on their ability to up regulate or down regulate BLR activity as stimulators or inhibitors, respectively (see page 56, lines 8-23). Further, the term "modulation" is well known in the art and also defined in the Webster's Dictionary to mean "regulating according to measure or proportion." Miriam Webster's Collegiate Dictionary, 10th Edition, 1993 Miriam-Webster Incorporated.

Furthermore, as indicated by copies of the issued claims in United States Patents **5,900,257**, **5,891,679**, and **5,888,747** (attached hereto as Appendices B,C, and D, respectively), the term "modulates" was well known and understood in the art at the time of the invention. Moreover, the presence of the term "modulates" in multiple issued claims[1], demonstrates that this term has been found by the United States Patent and Trademark Office to be clear and definite.

---

[1] A search of the claims of United States Patents issued since 1976 reveals that the term "modulates" appears in the claims of 3,227 patents.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

The Examiner also rejects claims 16 and 18 under 35 U.S.C. § 112, second paragraph as lacking antecedent basis for certain limitations in the claims. Applicants have amended the claims thereby rendering these rejections moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

Rejection of Claims 16-25 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 16-25 under 35 U.S.C. § 112, second paragraph as being, "incomplete for omitting essential steps, such omission amounting to a gap between the steps. Specifically, the Examiner is also of the opinion that:

> [t]he claims lack a positive recitation of method steps that recite a detection of the interaction between the BLR polypeptide and test compound. There are no steps which recite how to determine the modulation of BLR activity. There are no steps that incorporate the addition of necessary reagents to monitor the interaction. There are no comparison steps that compare the activity seen with and without the test compound to determine modulation. There are no identification steps that teach how to identify compounds. Finally there are no recited correlation steps that correlate the modulation of BLR activity to antibiotic resistance in a microbe.

Applicants traverse this rejection for the following reasons. Applicants have amended the claims to recite a correlation step between the modulation of BLR activity and the antibiotic resistance of bacteria. Further, Applicants have amended claim 16 to recite that the activity in the absence of the compound is compared to the activity in the presence of the compound. Moreover, as set forth above, Applicants' specification teaches several methods for determining whether a compound modulates BLR activity or binds to a BRL molecule. Applicants were the first to recognize the role of the BLR locus in modulating antibiotic resistance to antibiotics that affect peptidoglycan synthesis. Applicants argue that the claims set forth sufficient steps such that one of ordinary skill in the art could practice the methods as presently claimed and that Applicants should not be required to list steps of the methods which are not critical, but only those that are essential to the practice of the method. At the time the invention was made, one of ordinary skill in the art would have been able to practice the methods as presently claimed.

Therefore, Applicants contend that the amended claims do not fail to omit critical steps of the claimed methods. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 16-17 and 20-23 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 16-17 and 20-23 under 35 U.S.C. 102(b) as being anticipated by Boggs et al., (US Patent 5,883,074). Specifically, the Examiner is of the opinion that

> Boggs et al., teach methods of screening for compounds that potentiate the activity of antibacterial agents against bacteria. Beta-lactams are well known as antibacterial agents that are highly effective to treat bacterial infections (col. 1 lines 50-54). Such potentiators can reduce the Minimum Inhibitory Concentration (MIC) of an antibacterial agent which will completely inhibit growth of a susceptible strain (col. 4 lines 15-20). Potentiated antibacterial agents are beta-lactams, beta-lactam mimics, glycopeptides and the like (col. 6 lines 13-20). The potentiation screening assays determine whether or not a test compound such as unknown pharmacological, enhance the ability of the antibacterial agent to stop bacterial growth using high throughput whole cell assays (col. 11 lines 59-65). The assays combine beta-lactams and test compounds and thereby determine the MIC effect on bacteria, just as the instant claims require. Boggs et al., also teach in vitro application of potentiator assays (col. 15 lines 48-50).
>
> It is noted that the instant specification teaches BLR polypeptides as polypeptides sharing the ability to promote drug resistance in a cell (page 6). Likewise the prior art teaches that the antibacterial activity is the ability of a compound to effect the inhibition of growth of the bacterium (col. 7 lines 52-56). Therefore the BLP polypeptide of the instant specification and the polypeptide of the prior art are equivalent.

Applicant respectfully traverses this rejection. The instant claims are directed to methods for identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis in a bacterium by contacting a β–lactam-358 (BLR) polypeptide with a test compound.

For a prior art reference to anticipate in terms of 35 U.S.C. 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Boggs et al. teaches methods of screening for small molecules, termed potentiators, that make bacteria more susceptible to treatment with antibiotics. The reference fails to teach or suggest the use of BLR molecules in a screening assay to identify compounds that modulate resistance to antibiotics that affect peptidoglycan synthesis in a bacterium.

The BLR polypeptide and its role in modulating resistance to an antibiotic that affects peptidoglycan synthesis was first identified in the work presented in the instant application. The instant claims include the step of contacting a BLR polypeptide with a test compound to determine if that test compound is capable of modulating resistance to an antibiotic that affects peptidoglycan synthesis. Accordingly, Boggs et al. can not, and do not, teach a method of identifying a compound that modulates resistance to an antibiotic that affects peptidoglycan synthesis by contacting a BLR molecule with a test compound.

Since Boggs et al. does not teach each and every step of the instant methods, Boggs et al. does not anticipate the instant claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

References Made of Record

The Examiner has made the Cox et al. (US Patent No.: 5,672,497) and Watson et al. (US Patent No.: 5,998,159) references of record, and concluded that they were pertinent to Applicants' disclosure. Applicants would like to comment on these references.

Cox et al. teach a method of increasing the ability of a microbial cell to produce an antibiotic. The method involves transforming a bacterial cell with a gene that encodes an antibiotic synthetic enzyme. Cox et al. does not teach or suggest the use of a BLR polypeptide or nucleic acid molecule in a screening assay for identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis in a bacterium.

Watson et al. teach a method of identifying antibiotic agents that cause the accumulation of ppGpp in bacterial cells. Watson et al. does not teach or suggest the use of a BLR polypeptide or nucleic acid molecule in a screening assay for identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis in a bacterium.

Accordingly, Applicants disagree with the Examiner's assertion that the Cox et al. and Watson et al. references are pertinent to the claimed invention.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

Megan E. Williams, Esq.
Registration No. 43,270
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: September 4, 2003

Appendix A

16. **(Currently Amended)** A method for identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis in a bacterium comprising:

contacting a β–lactam-358 (BLR) polypeptide with a test compound;

determining the ability of the test compound to modulate an activity of a BLR polypeptide as compared to the activity in the absence of the compound, wherein the ability of the compound to modulate the activity of a BRL polypeptide indicates that the test compound modulates resistance to an antibiotic that affects peptidoglycan synthesis; and

selecting those compounds that modulate the activity of the BLR polypeptide to thereby identify compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis.

17. **(Currently Amended)** The method of claim 16, wherein the BLR polypeptide is present in a bacterial cell.

18. **(Currently Amended)** The method of claim 16, wherein the BLR polypeptide is heterologous to a cell in which it is present.

19. **(Currently Amended)** The method of claim 17, wherein the bacterial cell is an E. coli cell.

20. **(Currently amended)** The method of claim 17, wherein said step of determining comprises measuring the affect of the test compound on the ability of the bacterial cell to grow in the presence of an antibiotic that affects peptidoglycan synthesis.

21. **(Currently Amended)** The method of claim 20, wherein the antibiotic that affects peptidoglycan synthesis is selected from the group consisting of: a beta lactam, cycloserine, and bacitracin.

22. **(Currently Amended)** The method of claim 16, wherein said step of determining comprises measuring the efflux of the test compound or a marker compound from the cell.

23. **(Original)** The method of claim 16, wherein the BLR polypeptide is contacted with the test compound in vitro and the ability of the test compound to bind to the BLR polypeptide is determined.

24. **(Currently Amended)** A method for identifying compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis in a bacterium comprising:

contacting an isolated BLR nucleic acid molecule with a test compound;

determining the ability of the test compound to bind to the isolated BLR nucleic acid molecule, wherein the ability of the compound to bind the BRL nucleic acid molecule indicates that the test compound modulates resistance to an antibiotic that affects peptidoglycan synthesis; and

selecting those compounds that bind to the BLR nucleic acid molecule to thereby identify compounds that modulate resistance to an antibiotic that affects peptidoglycan synthesis.

25. **(Original)** The method of claim 24, wherein the BLR nucleic acid molecule comprises the nucleotide sequence shown in SEQ ID NO:1.

-continued

Methyl paraben		0.20
Sterile demineralized water	qs	100.00

EXAMPLE 2

Cleansing milk (Formula B):		
Lanthanum nitrate		0.5
Carbomer		0.40
Sodium hydroxide		0.10
Mineral oil Codex		5.00
Glycerol stearate		1.00
Cetyl alcohol		0.50
PEG 100 stearate		0.80
Methyl paraben		0.20
Perfume	qs	
Sterile demineralized water	qs	100.00

EXAMPLE 3

Care lotion (Formula C):		
Manganese chloride		15.00
Glycerol		2.00
Methyl paraben		0.15
Perfume	qs	
Sterile demineralized water	qs	100.00

EXAMPLE 4

Care cream (Formula D):		
Europium chloride		1.00
Glycerol stearate		1.00
PEG 100 stearate		1.00
Stearic acid		1.00
Cetyl alcohol		2.00
Soya bean oil		3.00
Palm oil		2.00
Cyclomethicone		2.00
Dimethicone		1.00
Polyacrylamide		0.20
Glycerol		3.00
Methyl paraben		0.20
Perfume	qs	
Sterile demineralized water	qs	100.00

EXAMPLE 5

Makeup removing lotion for the face (Formula E):		
Neodymium citrate		0.5
Antioxidant		0.05
Isopropanol		40.00
Preservative		0.30
Water	qs	100%

EXAMPLE 6

Face care gel (Formula F):	
Holmium chloride	0.5
Hydroxypropylcellulose (Klucel H marketed by Hercules)	1.00
Antioxidant	0.05
Isopropanol	40.00
Preservative	0.30
Water qs	100%

EXAMPLE 7

Care cream for solar erythema (oil-in-water emulsion) (Formula G):		
Neodymium chloride		5.00
Glycerol stearate		2.00
Polysorbate 60 (Tween 60 marketed by the company ICI)		1.00
Stearic acid		1.40
Glycyrrhetinic acid		2.00
Triethanolamine		0.70
Carbomer		0.40
Liquid fraction of shea butter		12.00
Sunflower oil		10.00
Antioxidant		0.05
Perfume		0.5
Preservative		0.30
Water	qs	100%

The following examples are of formulations illustrating the invention and particularly compositions comprising at least one lanthanide, manganese, tin or yttrium salt and an active species normally eliciting an irritant effect. These compositions were formulated simply by mixing the various components.

EXAMPLE 8

Composition 1: Gel for the treatment of acne:		
Manganese borate		5.00
All-trans-retinoid acid		0.05
Hydroxypropylcellulose (Klucel H)		1.00
Antioxidant		0.05
Isopropanol		40.00
Preservative		0.30
Water	qs	100%

EXAMPLE 9

Composition 2: Lotion for removing scars due to acne:		
Neodymium chloride		1.5
Glycolic acid		50.00
Hydroxypropylcellulose (Klucel H)		0.05
NaOH	qs pH =	2.80
Ethanol	qs	100%
Preservative		0.30

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof.

What is claimed is:

1. A method for the treatment of a mammalian disorder, a manifestation of which is selected from the group con-

sisting of (i) an excess in the synthesis of substance P, (ii) an excess in the release of substance P, and (iii) an excess in both the synthesis and release of substance P comprising administering to a mammalian organism in need of such treatment an effective substance P antagonist amount of at least one salt of yttrium, lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tin, manganese, or mixture thereof.

2. The method as defined by claim 1, comprising topically applying said at least one salt onto at least one of the skin, the hair, or the mucous membranes of said mammalian organism.

3. The method as defined by claim 1, wherein said mammalian disorder is selected from the group consisting of a disorder of the central nervous system, a respiratory disorder, an allergic syndrome, inflammation, pain, a gastrointestinal disorder, a skin disorder, fibroses, a collagen-maturation disorder, a cardiovascular disorder, a vasospastic disorder, an immunological disorder, a disorder of the urogenital tract, an ophthalmic and a pancreatic disorder.

4. The method as defined by claim 1, wherein said mammalian disorder is a cutaneous disorder.

5. The method as defined by claim 1, wherein said mammalian disorder comprises sensitive skin.

6. The method as defined by claim 1, which is used to treat at least one condition selected from the group consisting of cutaneous irritations, sores, erythemas, dysaesthetic sensations, warming sensations, pruritus of the skin, or pruritus of the mucous membranes.

7. The method as defined by claim 1, wherein said at least one salt is selected from the group consisting of a salt of neodymium, gadolinium, yttrium, and combinations thereof.

8. The method as defined by claim 1, wherein said at least one salt is selected from the group consisting of a chloride, borate, bicarbonate, carbonate, nitrate, hydroxide, sulfate, glycerophosphate, a salt of a fruit acid and a salt of an amino acid.

9. The method as defined by claim 8, wherein said at least one salt is a chloride or nitrate.

10. The method as defined by claim 1, comprising coadministering to said mammalian organism in combination with said substance P antagonist salt at least one other agent selected from the group consisting of (i) at least one antibacterial active agent, (ii) at least one active agent for combating parasites, (iii) at least one antifungal active agent, (iv) at least one antiviral active agent, at least one anti-inflammatory active agent, (v) at least one antipruriginous active agent, (vi) at least one anaesthetic active agent, (vii) at least one keratolytic active agent, (viii) at least one active agent for combating free radicals, (ix) at least one antiseborrhoiec active agent, (x) at least one antidandruff active agent, (xi) at least one antiacne active agents, (xii) at least one active agent which modulates cutaneous pigmentation (xiii) at least one active agent which modulates cutaneous proliferation and (xiv) at least one active agent which modulates cutaneous differentiation.

11. A cosmetic or pharmaceutical composition of matter suited for the treatment of a mammalian disorder, a manifestation of which is selected from the group consisting of (i) an excess in the synthesis of substance P (ii) an excess in the release of substance P, and (iii) an excess in the synthesis and release of substance P comprising an effective substance P antagonist amount of at least one salt selected from the group consisting of yttrium, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tin, manganese, and combinations thereof, contained in a cosmetically/pharmaceutically acceptable medium thereof.

12. The cosmetic or pharmaceutical composition as defined by claim 11, which is suitable for topical application.

13. The cosmetic or pharmaceutical composition as defined by claim 11, wherein said at least one salt comprises from 10^{-5}% to 20% of the total weight thereof.

14. The cosmetic or pharmaceutical composition as defined by claim 13, wherein said at least one salt comprises from 10^{-2}% to 15% of the total weight thereof.

15. The cosmetic or pharmaceutical composition as defined by claim 11, further comprising a normally skin-irritating amount of at least one skin irritant.

16. The cosmetic or pharmaceutical composition as defined by claim 11, further comprising at least one other antagonist selected from the group consisting of CGRP antagonist, histamine antagonist, interleukin-1 antagonist, TNF antagonist, and a different substance P antagonist than said at least one substance P antagonist salt.

17. The cosmetic or pharmaceutical composition as defined by claim 15, wherein said at least one skin irritant is selected from the group consisting of a surfactant, preservative, organic solvent, α-hydroxy acid, β-hydroxy acid, α-keto acid, β-keto acid, retinoid, anthralin, anthranoid, peroxide, minoxidil, lithium salt, antimetabolite, vitamin D, vitamin D derivative, hair dye, hair colorant, alcoholic perfume, antiperspirant, depilatory, permanent-wave, depigmenting active agent, and combinations thereof.

18. The cosmetic or pharmaceutical composition as defined by claim 11, further comprising an effective amount of at least one additional agent selected from the group consisting of at least one antibacterial active agent, at least one active agent for combating parasites, at least one antifungal active agent, at least one antiviral active agent, at least one anti-inflammatory active agent, at least one antipruriginous active agent, at least one anaesthetic active agent, at least one keratolytic active agent, at least one active agent for combating free radicals, at least one antiseborrhoeic active agent, at least one antidandruff active agent, at least one antiacne active agent, at least one active agent which modulates cutaneous pigmentation, at least one active agent which modulates cutaneous proliferation and at least one active agent which modulates cutaneous differentiation.

19. The cosmetic or pharmaceutical composition as defined by claim 11, which is in a form selected from the group consisting of a lotion, suspension, serum, eyedrops, capsules, granules, syrup, tablets, emulsion, milk, cream, gel, microcapsules, microparticles, vesicular dispersion, solution, foam, aerosol, cleansing bar, soap, toothpaste, shampoo, and hair care formulation.

* * * * *

-continued

Asp	Gln	Leu	Ser	Ala	Glu	Val	Asn	Leu	Pro	Lys	Tyr	Leu	Asp	Phe	Ala				
	130					135					140								
Glu	Ser	Gly	Gln	Val	Tyr	Phe	Gly	Val	Ile	Ala	Leu								
145					150					155									

We claim:

1. A human or murine tumor necrosis factor mutein selected from the group consisting of:

a TNF mutein wherein the amino acid region 105–110, or a part thereof, is deleted,

a TNF mutein wherein at least one amino acid of the amino acid region 105–110 is in the D configuration,

a TNF mutein wherein amino acid 105, 106, 107 or 110 is substituted,

a TNF mutein wherein the combination of amino acid 105 and 110, 107 and 110, 105 and 110, or, 105 and 107 and 110, is substituted,

which has at least one of the following activites:

modulates the lectin-like activities of TNF,

reduces the toxic activity of TNF,

modulates the inflammatory cytokine-inducing capacity of TNF, and

reduces the metastasis-promoting activity of TNF; and

increases the serum half-live of TNF, and

retains the tumoricidal activity of TNF, and

which is characterized in that

amino acid 1 to 8 of said human TNF is replaced by a sequence within the region amino acid 5 to 30 of laminin, and,

amino acid 105 of said human TNF mutein is not proline or isoleucine, amino acid 106 of said human TNF mutein is not serine and amino acid 110 of said human TNF mutein is not lysine;

or a salt of said muteins.

2. A TNF mutein according to claim 1, characterized in that the lectin-like activities are modulated with respect to TNF-α.

3. A TNF mutein according to claim 1, characterized in that the lectin-like activities are increased with respect to TNF-α.

4. A TNF mutein according to claim 1, characterized in that the lectin-like activities are reduced with respect to TNF-α.

5. A TNF mutein according to claim 1, characterized in that the toxic activity is reduced with respect to TNF-α.

6. A TNF mutein according to claim 1, characterized in that the inflammatory cytokine inducing capacities are modulated with respect to TNF-α.

7. A TNF mutein according to claim 1, characterized in that the inflammatory cytokine inducing capacities are increased with respect to TNF-α.

8. A TNF mutein according to claim 1 characterized in that the inflammatory cytokine inducing capacities are reduced with respect to TNF-α.

9. A TNF mutein according to claim 1 characterized in that the adhesion molecule inducing capacities are modulated with respect to TNF-α.

10. A TNF mutein according to claim 1, characterized in that the adhesion molecule inducing capacities are reduced with respect to TNF-α.

11. A TNF mutein according to claim 1 characterized in that the adhesion molecule inducing capacities are increased with respect to TNF-α.

12. A TNF mutein according to claim 1 characterized in that the metastasis promoting activity is reduced with respect to TNF-α.

13. A TNF mutein according to claim 1 characterized in that the tumoricidal activity is retained with respect to TNF-α.

14. A TNF mutein according to claim 1 characterized in that the tumoricidal activity is reduced with respect to TNF-α.

15. A TNF mutein according to claim 1 characterized in it shows an increased half life time with respect to TNF-α.

16. A TNF mutein according to claim 1 characterized in that at least part of the region extending from amino acid positions 105 to 110 of TNF-α, or the complete region corresponding to amino acid positions 105 to 110 of TNF-α has been deleted.

17. A TNF mutein according to claim 1 characterized in that at least one of the amino acids in the region extending from amino acids 105 to 110 of TNF-α, has been mutated or deleted.

18. A nucleic acid sequence encoding any of the polypeptides according to claim 1.

19. A process for the preparation of a polypeptide according to claim 1, comprising the steps of:

transformation of an appropriate cellular host with a vector selected from the group consisting of a plasmid, a cosmid, a phage and a virus, in which a nucleic acid sequence coding for said polypeptide has been inserted, to form an insert, under the control of regulatory elements selected from the group consisting of a promoter recognized by the polymerases of the cellular host and, a ribosome binding site enabling the expression in said cellular host of said nucleic acid sequence,

culture of said transformed cellular host under conditions enabling the expression of said insert; and

recovering said polypeptide.

20. Cells transfected with a nucleic acid according to claim 18 coding for the TNF muteins, said nucleic acid being inserted into any suitable vector, with said cells being preferably autologus cells derived from a patient to be treated with such compositions; and with said vector-insert combination being constructed in such a way as to allow continuous expression of the TNF mutein at either a constant level, or at a level which can be modified, depending on the exact nature of the vector used to make the vector-insert combination.

21. The TNF mutein of claim 16 wherein at least the region covering amino acid positions 105 to 110 has been deleted.

22. The TNF mutein of claim 17 wherein at least one of the amino acids in the region extending from amino acids 105 to 110 has been mutated or deleted.

* * * * *

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGTTGCGGA GGGTGGGCCT GGGAGGGGTG GTGGCCATTT TTTGTCTACC CTACTGAGAA 60

GGGCGTAGGC GCCGTGCTTT TGCTCCCCGC GCGCTGTTTT TCTCGCTGAC TTTCAGCGGG 120

CGGAAAAGCC TCGGCCTGCC GCCTTCCACC GTTCATTCTA GAGCAAACAA AAAATGTCAG 180

CTGCTGGCCC GTTCGCCCCT CCCGGGGACC TGCGGCGGGT CGCCTGCCCA GCCCCCGAAC 240

CCCGCCTGGA GGCCGCGGTC GGCCCGGGGC TTCTCCGGAG GCACCCACTG CCACCGCGAA 300

GAGTTGGGCT CTGTCAGCCG CGGGTCTCTC GGGGGCGAGG GCGAGGTTCA GGCCTTTCAG 360

GCCGCAGGAA GAGGAACGGA GCGAGTCCCC GCGCGCGGCG CGATTCCCTG AGCTGTGGGA 420

CGTGCACCCA GGACTCGGCT CACACATGCA GTTCGCTTTC CTGTTGGTGG GGGGAACGCC 480

GATCGTGCGC ATCCGTCACC CCTCGCCGGC AGTGGGGGCT TGTGAACCCC CAAACCTG 538

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: Not Relevant
(D) TOPOLOGY: Not Relevant

(i i) MOLECULE TYPE: peptide

(i x) FEATURE:
(A) NAME/KEY: Peptide
(B) LOCATION: 5..13
(D) OTHER INFORMATION: /note= "Xaa represents isoleucine or leucine"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Glu Ala Ala Thr Xaa Asp Xaa Pro Gln Gln Gly Ala Asn Lys
1 5 10

What is claimed is:

1. A method of screening for an agent which modulates the binding of a human telomerase to a binding target said method comprising the steps of:

translating an isolated nucleic acid comprising SEQ ID NO:3, or a portion thereof at least 36 nucleotides in length and immediately flanked by a native flanking region fewer than 10 kb and encoding a telomerase protein p105 (SEQ ID NO:1) domain having human telomerase-specific activity, to obtain a human telomerase protein domain;

incubating a mixture comprising:

a telomerase or telomerase protein comprising said domain,

a binding target of said telomerase protein, and

a candidate agent;

under conditions whereby, but for the presence of said agent, said telomerase or telomerase protein specifically binds said binding target at a reference affinity;

detecting the binding affinity of said telomerase or telomerase protein to said binding target to determine an agent-biased affinity,

wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said telomerase or telomerase protein to said binding target.

2. A method according to claim 1, wherein said binding target is a substrate of said telomerase and said reference and agent-biased binding affinity are each detected as the polymerization by said telomerase of a nucleic acid on said substrate.

3. A method according to claim 1, wherein said domain specifically binds at least one of the telomerase RNA of SEQ ID NO:6, a telomerase subunit, substrate, agonist, antagonist, chaperone, regulatory protein or cytoskeletal protein.

4. A method according to claim 1, wherein the portion encodes at least one of SEQ ID NO:1, residues 5–81, 115–192, 336–420 and 487–578.

5. A method of screening for an agent which modulates the binding of a human telomerase to a binding target, said method comprising the steps of:

translating an isolated nucleic acid comprising a portion of SEQ ID NO:3, nucteotides 1–2345, at least 36 nucleotides in length and immediately flanked by a native flanking region fewer than 10 kb and which specifically hybridizes with a nucleic acid having the sequence defined by SEQ ID NO:3 under low stringent conditions, to obtain a human telomerase protein domain;

incubating a mixture comprising:

a telomerase or telomerase protein comprising said domain,

a binding target of said telomerase protein, and

a candidate agent;

under conditions whereby, but for the presence of said agent, said telomerase or telomerase protein specifically binds said binding target at a reference affinity;

detecting the binding affinity of said telomerase or telomerase protein to said binding target to determine an agent-biased affinity,

wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said telomerase or telomerase protein to said binding target.

6. A method according to claim 5, wherein the portion is at least 60 nucleotides in length.

7. A method of screening for an agent which modulates the binding of a human telomerase to a binding target, said method comprising the steps of:

translating a recombinant nucleic acid consisting of an open reading frame comprising SEQ ID NO:3, or a portion thereof at least 60 nucleotides in length sufficient to encode a telomerase protein p105 (SEQ ID NO:1) domain at least 20 residues in length and having human telomerase-specific activity, to obtain a human telomerase protein domain;

incubating a mixture comprising:

a telomerase or telomerase protein comprising said domain,

a binding target of said telomerase protein, and

a candidate agent;

under conditions whereby, but for the presence of said agent, said telomerase or telomerase protein specifically binds said binding target at a reference affinity;

detecting the binding affinity of said telomerase or telomerase protein to said binding target to determine an agent-biased affinity,

wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said telomerase or telomerase protein to said binding target.

8. A method according to claim 7, wherein said open reading frome comprises SEQ ID NO:3, nucleotides 97–2370.

* * * * *